



PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

see form PCT/ISA/220

716538

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

22 DEC 2005 / 22 JAN 2006

Date of mailing

(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION

See paragraph 2 below

International application No.
PCT/US2005/007507

International filing date (day/month/year)
09.03.2005

Priority date (day/month/year)
22.03.2004

International Patent Classification (IPC) or both national classification and IPC
A61K31/4406, A61K31/44, C07D213/16, C07D213/18, C07D213/85, C07D213/89, C07D213/61, C07D213/65,

Applicant
ELI LILLY AND COMPANY

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

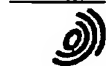
If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2005/007507

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
☐ a sequence listing
☐ table(s) related to the sequence listing
 - b. format of material:
☐ in written format
☐ in computer readable form
 - c. time of filing/furnishing:
☐ contained in the international application as filed.
☐ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application,
- ☒ claims Nos. 1-4

because:

- ☒ the said international application, or the said claims Nos. 1-4 relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☒ no international search report has been established for the whole application or for said claims Nos. 1-4
- ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:
 - the written form ☐ has not been furnished
 - ☐ does not comply with the standard
 - the computer readable form ☐ has not been furnished
 - ☐ does not comply with the standard
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.
- ☐ See separate sheet for further details

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2005/007507

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	
	No: Claims	5-13,16,18-20,22
Inventive step (IS)	Yes: Claims	1-25(partly)
	No: Claims	
Industrial applicability (IA)	Yes: Claims	5-25
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43bis.1 and 70.10)

and /or

2. Non-written disclosures (Rules 43bis.1 and 70.9)

see form 210

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The claims 1-4 are directed to methods of treatment of a disorder defined in functional terms that are not considered to be clear in the sense of Article 6 PCT. The therapeutic application is functionally defined by a mechanism of action which does not allow any practical application in the form of a defined real treatment of a pathological condition. The search was carried out only for those diseases listed in the application, page 8, lines 26-28, such that this preliminary opinion is only valid for the use in the treatment of such diseases. Furthermore claims 1-4 also relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The following documents cited in the search report are referred to in this communication;

- D1: WO 01/90101 A (AVENTIS PHARMACEUTICALS PRODUCTS INC; ASTLES, PETER, C; EASTWOOD, PAUL) 29 November 2001 (2001-11-29)
- D2: HOEKSTRA ET AL: "Potent, Orally Active GPIIb/IIIa Antagonists Containing a Nipecotic Acid Subunit. Structure-Activity Studies Leading to the Discovery of RWJ-53308" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 42, no. 25, 1999, pages 5254-5265, XP002142349 ISSN: 0022-2623
- D3: WO 96/01825 A (FUJISAWA PHARMACEUTICAL CO., LTD; HEMMI, MITSUE +HF; SHIMAZAKI, NORIHI) 25 January 1996 (1996-01-25)
- D4: WO 97/24355 A (FUJISAWA PHARMACEUTICAL CO., LTD; SHIMAZAKI, NORIHIKO; SAWADA, AKIHIKO) 10 July 1997 (1997-07-10)
- D5: NOVAK, ZOLTAN ET AL: "Tandem Sonogashira coupling: An efficient tool

- for the synthesis of diarylalkynes" ORGANIC LETTERS , 6(26), 4917-4920
CODEN: ORLEF7; ISSN: 1523-7060, 12 February 2004 (2004-02-12),
XP002331794
- D6: RAJADURAI, CHANDRASEKAR ET AL: "Study on the Heteroatom Influence
in Pyridine-Based Nitronyl Nitroxide Biradicals with Phenylethynyl Spacers
on the Molecular Ground State" JOURNAL OF ORGANIC CHEMISTRY ,
68(26), 9907-9915 CODEN: JOCEAH; ISSN: 0022-3263, 2003,
XP002331797
- D7: KATRITZKY, ALAN R. ET AL: "The preparation of diarylacetylenes via
diphenyl (benzotriazol-1-yl)(aryl)methylphosphonates" ARKIVOC
(GAINESVILLE, FL, UNITED STATES) , (13), 17-27 CODEN: AGFUAR
URL: HTTP://WWW.ARKAT-USA.ORG/ARK/JOURNAL/2002/
KARABATSOS/GK-706F/706F.PDF, 2002, XP002331798
- D8: WO 03/035620 A (ASAHI KASEI KABUSHIKI KAISHA; MIYOSHI, SHIRO;
OGAWA, KOHEI) 1 May 2003 (2003-05-01)
- D9: WANG, ZHIYONG ET AL: "An improved coupling reaction for the
preparation of pyridylethynyl benzonitrile compounds" CHINESE SCIENCE
BULLETIN , 46(19), 1606-1608 CODEN: CSBUEF; ISSN: 1001-6538, 2001,
XP009048572
- D10: LIN, WENBIN ET AL: "Three-Dimensional Manganese(II) Coordination
Polymers Based on m-Pyridinecarboxylates: Synthesis, X-ray
Structures, and Magnetic Properties" INORGANIC CHEMISTRY ,
39(18), 4169-4173 CODEN: INOCAJ; ISSN: 0020-1669, 2000,
XP002331799
- D11: EP-A-0 436 398 (ALLERGAN, INC) 10 July 1991 (1991-07-10)
- D12: WO 01/16121 A (MERCK & CO., INC; COSFORD, NICHOLAS, D., P;
MCDONALD, IAN, A; BLEICHER) 8 March 2001 (2001-03-08)
- D13: WO 01/72291 A (THE VICTORIA UNIVERSITY OF MANCHESTER;
BROTCHIE, JONATHAN; HILL, MICHA) 4 October 2001 (2001-10-04)

With regard to the requirement for novelty (Article 33(2) of the PCT), the compounds of claims 5-13, 16, 18-20, 22 are not novel due to the disclosures of D1-D11 (see the relevant passages in the search report), as all of these documents disclose either specific compounds falling within the scope of claim 5 (D1-D10), or a general formula

which overlaps with that of claim 5 (see D11). The compound excluded from claim 5 is known from ChemCats, RN number 845266-26-4.

For the claims 1-4, which are examined as first medical use claims (see point III above), none of the documents discloses the use of such compounds in pain, psychosis, stroke, Alzheimer's, anxiety, depression, drug dependency or cognitive impairment, and these uses appear to be novel.

With regard to the requirement for inventive step (Article 33(3) of the PCT), the problem underlying the present application was the provision of further novel compounds with mGlu5 receptor activity. The solution provided by the Applicant is the compounds of formula I. The man skilled in the art, faced with this problem, would have been aware from D13 that the compounds 2-methyl-6-(phenylethynyl or ethenyl) pyridine have this activity, and from D12 that compounds of the general formula described therein wherein L is alkenylene or alkynylene, attached in the 2-position to the pyridyl have this activity, but would have had no direct incentive to prepare the pyrid-3-yl compounds of the present application, expecting them to have the desired activity. Thus an inventive step could be acknowledged for the novel subject matter of claims 1-25.

Re Item VI

Certain documents cited

Certain published documents

Application No Patent No	Publication date (day/month/year)	Filing date (day/month/year)	Priority date (valid claim) (day/month/year)
WO2004067002	12.08.2004	30.01.2004	30.01.2003
SORENSEN U S ET AL: "Copper-free palladium-catalyzed sonogashira-type coupling of aryl halides and 1-aryl-2-(trimethylsilyl)acetylenes" TETRAHEDRON, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 61, no. 10, 7 March 2005 (2005-03-07), pages 2697-2703, XP004756737 ISSN: 0040-4020			

WOLF, CHRISTIAN ET AL: "Palladium-phosphinous acid-catalyzed Sonogashira cross-coupling reactions in water" ORGANIC & BIOMOLECULAR CHEMISTRY , 2(15), 2161-2164 CODEN: OBCRAK; ISSN: 1477-0520, 30 June 2004 (2004-06-30), XP002331795

HE H ET AL: "Copper-catalyzed cross-coupling of aryl iodides and aryl acetylenes using microwave heating" TETRAHEDRON LETTERS, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 45, no. 16, 12 April 2004 (2004-04-12), pages 3237-3239, XP004498987 ISSN: 0040-4039

PENNEY J M ET AL: "Alkynylation of benzonitriles via nickel catalyzed C-C bond activation" TETRAHEDRON LETTERS, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 45, no. 25, 14 June 2004 (2004-06-14), pages 4989-4992, XP004510991 ISSN: 0040-4039

SUN, SHIH-SHENG ET AL: "Directed Assembly of Transition-Metal-Coordinated Molecular Loops and Squares from Salen-Type Components. Examples of Metalation-Controlled Structural Conversion" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY , 126(20), 6314-6326 CODEN: JACSAT; ISSN: 0002-7863, 2004, XP002331796

CRYSTAL GROWTH AND DESIGN, vol. 5, no. 2, 14 September 2004 (2004-09-14), pages 609-616, XP002331800